

PSJ15 Exh 38

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The History & Medical Basis of Methadone in the Treatment of Opioid Addiction

What is this presentation about?

- Where, when, and why was methadone developed?
- How was methadone first used?
- How did it come to be used for treating opioid addiction?
- How does methadone work?
- Why is methadone effective for treating opioid addiction?

Historic Roots of Opioid Addiction

- Use of opioids dates back centuries.
- In 19th century U.S. opioid medicines commonly available.
- After 1900 opioid addiction rose, leading to restrictive legislation.
- Opioid abuse criminalized; treatment needed for those addicted.



Opioids were once common ingredients in patent medicines available to anyone.

Dealing With Opioid Addiction

- Specialty clinics offered opioid detox or maintenance meds: heroin, morphine, cocaine.
 - By 1923 all were closed by federal government.
- In 1930's, two federal "narcotic treatment programs" established: Lexington; Fort Worth.
 - Mainly provided detox and were largely failures.
- During 1950's, drug-free therapeutic communities were founded (e.g., Synanon).
- By 1960's, there were few options for treatment; opioid-addicted persons were largely considered "morally bankrupt criminals."

Truth or Myth?

Methadone was developed by the Nazis during WW II?

It was urgently needed as a morphine substitute?

Methadone – originally named Dolophine® – was named after Adolf Hitler?

It was first used in the U.S. for heroin withdrawal?

Methadone Discovery in Germany

- Developed in late 1930's by chemists at IG Farberindustrie.
- Not part of a Nazi attempt to replace opium supplies.
- Called "Hoechst 10820", later named Polamidon®.
- Not effectively used as analgesic during War.



Patent filed in 1941.

Post-War Adoption Worldwide

- After World War II, the formula for methadone became available worldwide.
- It was found to be a potent analgesic, although little was known about proper Rx.
- Dolophine® – a later trade name – did not come from “Adolf” Hitler.
 - Most likely derived from the French *dolor* (pain) and *fin* (end).

Early Methadone Analgesia

- 1947 – Approved as analgesic in U.S.¹
- Original uses were: migraine, menstrual or labor pain, painful nerve disorders, cancer, and others.
- In late 1940's – 1950's, deaths associated with methadone due to improper Rx and/or use.
- By early 1960's, methadone had fallen into disuse due to perceived toxicity and its potential for producing dependence.
 - Only relatively recently has there renewed interest in using methadone as an analgesic.

1. <http://www.usdoj.gov/dea/concern/m.html>

Development of Methadone Maintenance Treatment (MMT) in NY

- Research started in 1963 by Dole & Nyswander at Rockefeller University.
- Believed opioid addiction was driven by metabolic defect or brain damage from opioid abuse.
- Methadone: long-acting, oral administration, previously used.



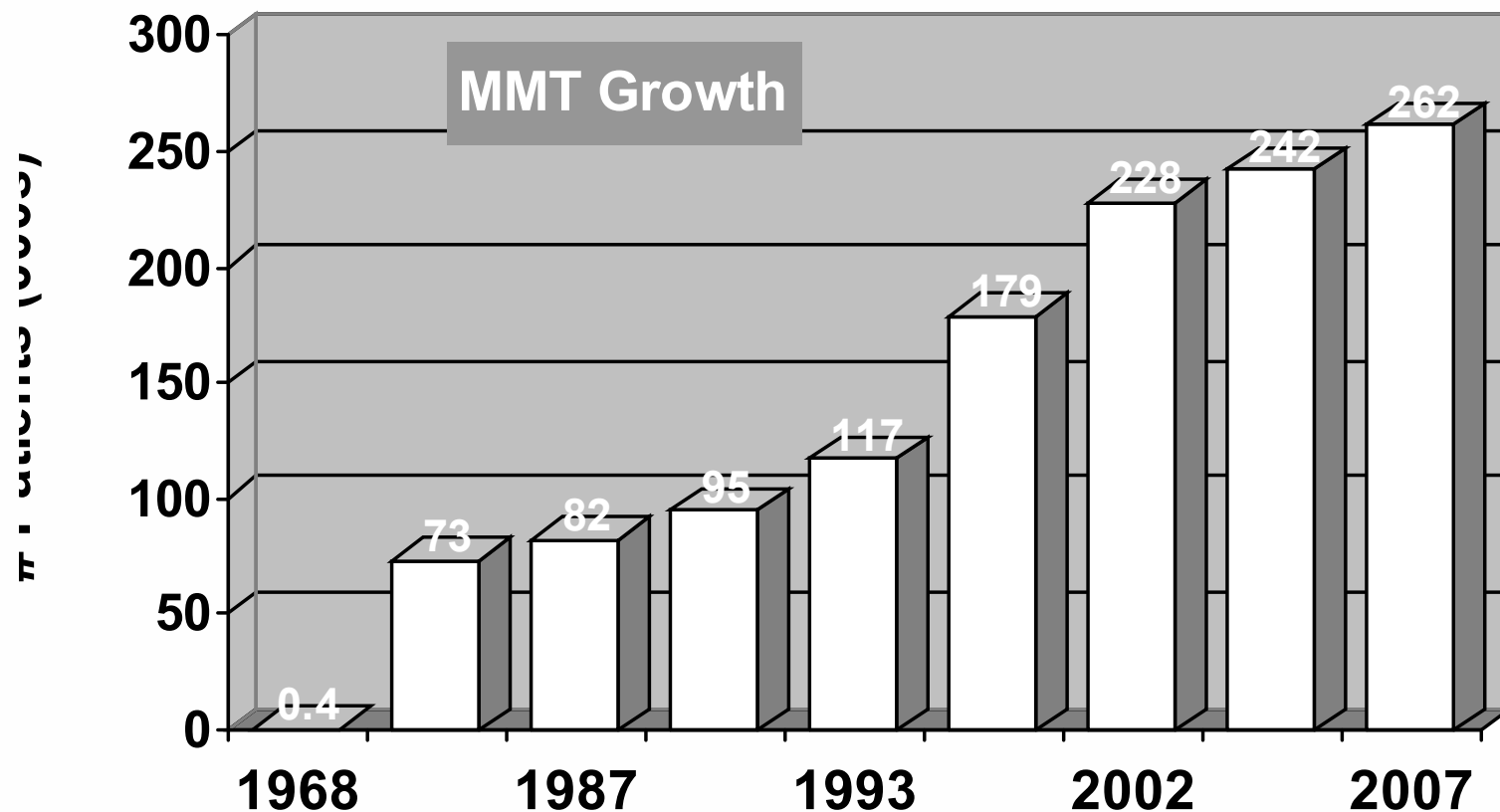
Leaders in MMT at a conference in the mid-1980s. Left to right: Julio A. Martinez, then Commissioner of New York State's DSAS, now ODAS; standing is Mark Parrino, currently President of AATOD; Jim O'Hanlon, an Assistant Commissioner of DSAS/ODAS; Beny Primm, MD; Erica Spitz, Director of the Drug Abuse Project at the New York Urban Coalition (now defunct); Lazette McCants, Erica's Assistant Director; Charlie LaPorte, Deputy Commissioner for Methadone Services of DSAS/ODAS; seated are Vincent P. Dole, MD, and Marie E. Nyswander, MD.

MMT Successes & Challenges

- 1964-1968: 1,139 patients treated in MMT with successful outcomes. (industry estimates)¹
- Created unrealistically high expectations.
- Rapid expansion of MMT clinics resulted in poor quality control and methadone diversion.
- By the 1980's MMT funding was curtailed.
- However, emerging addiction-related epidemics (e.g., HIV/AIDS) caused renewed interest in MMT to fight spread of needle-borne disease.

1. http://www.ajph.org/cgi/reprint/64/12_Suppl/44.pdf.

Patient Growth in MMT₁



Increases in patients and clinics during more than 40 years still do not fully meet the need for treatment.



1. AMTA 1999; Dole 1998, 1999; Federal Register 1999, 2001.

MMT Program Regulation

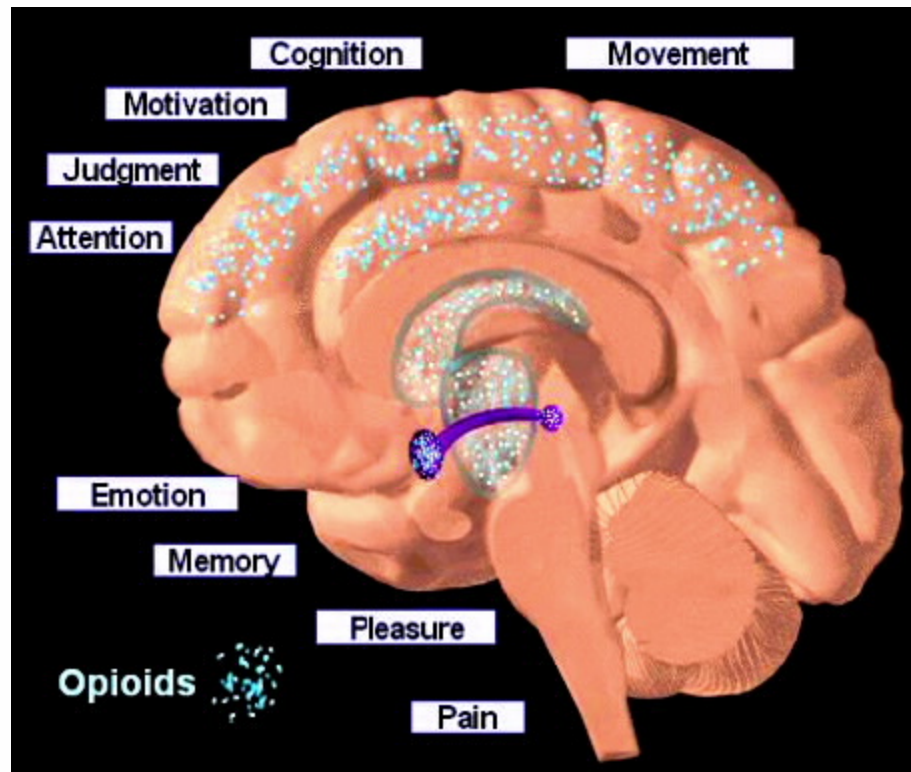
- Early resistance to MMT came from many directions and agencies.
- Attitudes hardened into regulation by FDA in 1973, imposing reporting requirements.
- By 1990's – DEA, FDA, and SAMHSA were involved in MMT regulation.
 - Plus, state, local, and community agencies.
- In 2001, federal regulations were replaced by a formal accreditation process under CSAT.
 - Allows medical discretion in treatment decisions.

Medical Basis of Methadone

An opioid well suited for maintenance treatment

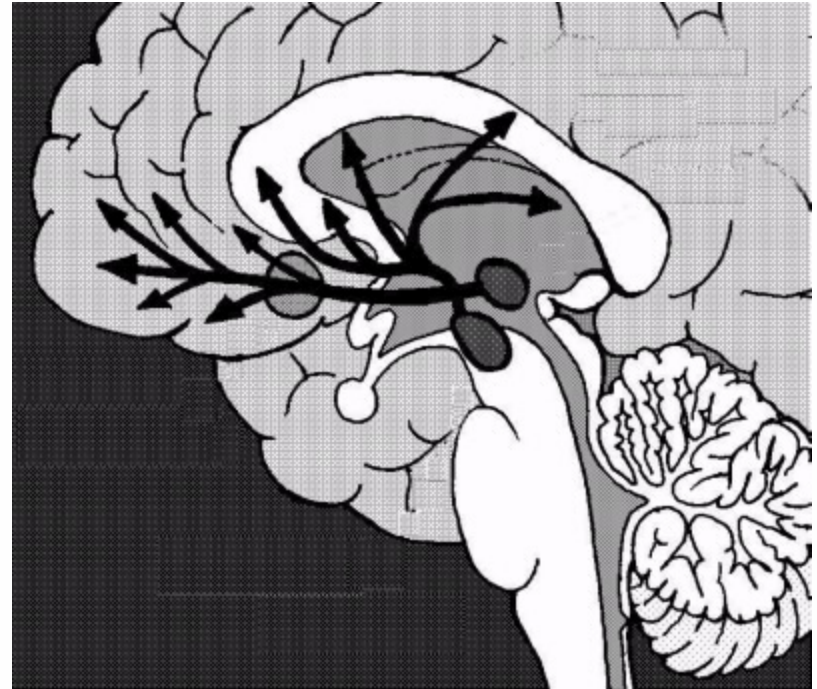
Opioids Affect Many Brain Areas

- Endogenous opioids influence many critical brain functions.
- External opioids can flood key areas with excessive dopamine.
 - Normal chemical balance is disrupted.



Dopamine “Reward Pathways”

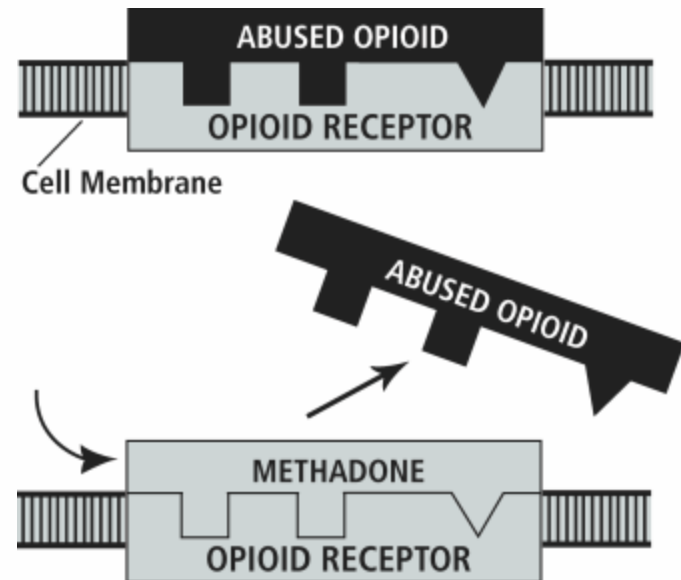
- Reward pathway arises deep within the brain.
- Dopamine-producing neurons project forward into cognitive centers.
- Excess dopamine, due to opioid effects, impairs willful control of emotions and thoughts.



When abused, opioids “hijack” critical brain functions, leading to continued use of opioids even when the person expresses a desire to stop.

Methadone at Opioid Receptors¹

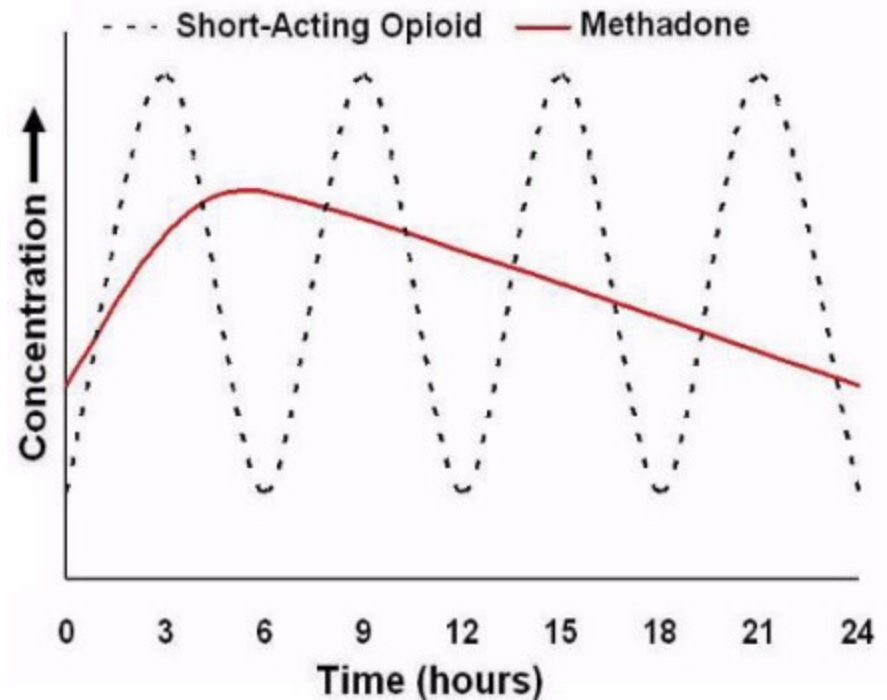
- External opioids fit into mu-opioid receptors like keys in locks to activate neurons.
- Methadone fits into the receptors and binds tightly. Other opioids may be blocked.



After chronic opioid abuse, if all extrinsic opioid is exhausted from receptors and not replaced, withdrawal and craving begin.

Opioid Actions

- Short-acting opioids can produce wide swings in effect during the day.
- Methadone provides near steady-state serum blood levels during dosing period.



The goal of Methadone Maintenance is to avoid withdrawal and euphoria, as its concentration remains relatively stable during a 24 hour period.

Bio-Psycho-Socio Model in MMT

The bio-psycho-socio model of addiction reasons that a combination of biological, psychological, and socio-environmental factors play a significant role in the addictive process.

- Biological: physical, biochemical, and genetics
- Psychological: thoughts, emotions, behaviors, and personality traits.
- Socio-environmental: family, community/school, peer/social attitudes, and drug availability.

1. <http://www.samhsa.gov/LitReviews/SAMHSASUM189.html>

MMT Goals

- **Ultimate goal of drug addiction treatment is to enable an individual to achieve lasting abstinence from an abused substance. (Phil disagrees with this, maybe achieve a lifestyle that sustains normalcy or something of that nature)._{PM}**
- Immediate goals:
 - Reduce drug abuse.
 - Improve the patient's ability to function.
 - Minimize the medical and social complications of drug abuse and addiction.

Benefits of Successful MMT

- When adequate doses are achieved, does not make patient “high” or somnolent.
- Limits exposure to needle-borne infections, by taking medication orally
- Eliminates opioid withdrawal and craving.
- Cross-tolerance may make other opioids less desirable and drug-seeking behavior may be decreased.
- Once stability is achieved, there is usually no need for constant dose increases.
- Properly implemented, MMT has a manageable safety profile.

Benefits of *Ongoing* MMT

- Maintenance therapy is a positive
 - Many patients are unable to complete methadone medically-supervised withdrawal (MSW) and may leave treatment entirely.¹
 - After MSW alone, relatively few patients continue drug-free without relapse to drug abuse.
- Significant quality of life and health benefits are gained by continuing MMT.
- MMT also reduces risk of needle-borne infection and premature death, compared with relapse to illicit opioid abuse.

1. Backmund et al. 2001; Bell and Zador 2000

Treatment Outcomes

- Success and failure rates are difficult to track
 - Transient nature of the patient population.
 - Incomplete historical data.
- In the criminal justice system
 - Helps reduce crime by drug abusers and helps limit the spread of HIV, all forms of hepatitis, and other communicable diseases.
 - NIDA estimates that “for every dollar spent on addiction treatment programs, there is a \$4 to \$7 reduction in the cost of drug-related crimes.
 - Some outpatient programs see total savings exceeding costs by a ratio of 12:1.¹
- NIDA further states that “untreated substance abusing offenders are more likely to relapse to drug abuse and return to criminal behavior.”
 - Treatment offers the best alternative for interrupting the drug abuse/criminal justice cycle for offenders with drug abuse problems.”
- Some studies have shown that treatment can cut drug abuse in half, reduce criminal activity up to 80%, and reduce arrests up to 64%.¹

1. <http://international.drugabuse.gov/collaboration/PDFs/partb.pdf>

Methadone Truth or Myth?

“Myth-understandings” about methadone and MMT have created fear and anxiety through the years.

Myth: MMT Merely Substitutes One Addictive Drug With Another?

Truth:

- MMT uses medication (methadone) as part of a treatment program to overcome the need for abused opioids.
- Methadone pharmacologic actions are different than other opioids; not a mere substitute.
- Addictive, opioid-seeking, behaviors are likely to be substantially reduced or eliminated.
- MMT benefits overshadow reliance on a dependency-producing medication.
 - Consequences of untreated opioid addiction include: destitution, prison, disease, and/or early death.

Myth: Methadone Keeps Patients “High”?

Truth:

- At appropriate levels in MMT patients, methadone allows normal function – no euphoria or sedation.
- Adequate doses also avoid extremes of intoxication *or* withdrawal.
- After dosing, some patients may “sense” the onset of methadone effects or have vague feelings of “well-being” (which soon wear off after blood levels peak).

Myth: MMT Patients Keep Using Other Drugs And Alcohol?

Truth:

- MMT is not a “cure” for addiction.
 - It addresses abused opioid withdrawal and craving.
- Pharmacologically methadone has little direct impact on alcohol, cocaine, etc. usage
- However, with *effective dosage* of methadone, and therapy in MMT, most patients *do* eliminate or reduce ongoing alcohol and other drug abuse.¹
- Counseling, psychosocial therapy, and 12-Step groups are important in dealing with problems of continuing drug abuse.²

1. Goldsmith et al. 1984; McCann et al. 1994; Velten 1992.

2. Zweben and Payte 1990; Zweben and Sorensen 1988.

Myth: Methadone Gets in Bones, and Rots Teeth?

Truth:

- Many MMT patients have bone/joint aches and/or tooth decay – hence, this myth.
- Most cases can be explained either by...
 - Illness (e.g., arthritis, flu, etc.)
 - Temporary opioid withdrawal during stabilization or dose adjustments.
 - Past or current neglect of dental or physical health.
- There is no scientific evidence of methadone affecting bone or tooth structures.

Myth: Methadone is Bad for Pregnant Women and Their Newborns?

Truth:

- Pregnant MMT patients can deliver healthy babies.
- Newborns may experience withdrawal, which can be successfully treated.
- Compared with untreated opioid addiction, MMT has demonstrated significant benefits for mothers & their infants.¹

1. Berghella et al. 2003.

Myth: Low-Dose Methadone is Best?

Truth:

- This old approach stems from stigmatization of methadone, and belief that lower doses would make eventual withdrawal easier.
- Clinical experience has consistently shown that patients receiving higher doses exhibit better outcomes.¹
- How much is “high enough” depends on individual patient needs.
- Minimum/Maximum doses dictated by a clinic’s policy rather than patient specific medical criteria, are contrary to current federal regulations.

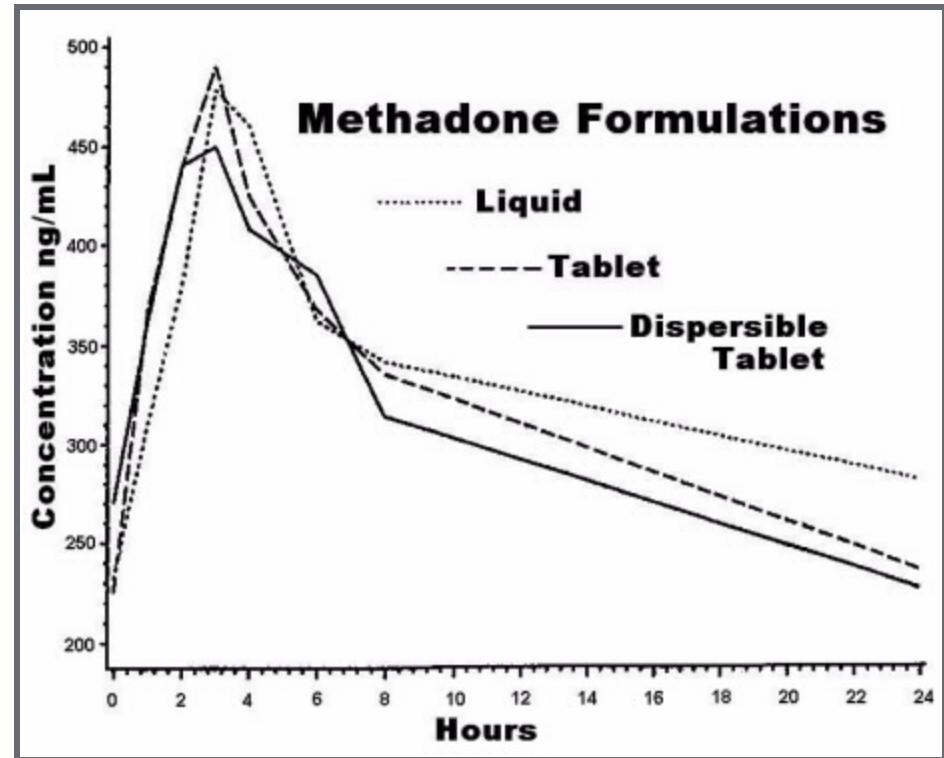


1. Goldsmith et al. 1984; Leavitt 2003; Leavitt et al. 2000.

Myth: Methadone Tablets Less Effective Than Oral Concentrate? Or, Vice Versa?

Truth:

In a clinical trial (n=18), 3 methadone formulations were found equivalent, both pharmacologically and in terms of patient-reported opioid-withdrawal symptoms.¹



1. Gourevitch MN, Hartel D, Tenore P, et al. Three oral formulations of methadone. A clinical and pharmacodynamic comparison. *J Substance Abuse Treatment*. 1999;17(3):237-241

Conclusions

- **Methadone used in millions of patients – 60+ years (40+ MMT).**
- **Thoroughly studied and tightly regulated**
- **Demonstrated as effective, with acceptable safety profile when properly prescribed and used.**
- **MMT is designed to reduce opioid-relapse, facilitates therapy, helps enable patients to get their lives back together.**

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